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Drug-Associated Agranulocytosis: 20 Years of Reporting in The Netherlands (1974–1994)

M.M. van der Klauw,[1,2] J.H.P. Wilson,[2] and B.H.Ch. Stricker[1,3]*

[1]Drug Safety Unit, Inspectorate for Health Care, Rijswijk, The Netherlands
[2]Department of Internal Medicine II, Erasmus University Medical School, Rotterdam, The Netherlands
[3]Pharmacoepidemiology Unit, Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands

In this descriptive study, all 425 reports were included concerning drug-associated agranulocytosis as registered between 1974 and 1994 in the files of the Drug Safety Unit of the Dutch Inspectorate for Health Care. All reports were analysed as to the probability of agranulocytosis or neutropenia according to previously defined criteria. Subsequently, the causal relationship between exposure and outcome was assessed. It concerned 149 men and 271 women. One hundred and twelve reports were unclassifiable because age, gender, or total number of leukocytes at the time of reaction were unknown. In 100 reports agranulocytosis was probable, in 78 possible, in 8 reports neutropenia was probable, in 20 reports neutropenia was possible, and in 107 reports agranulocytosis or neutropenia were unlikely. In the 13 reports of probable agranulocytosis or neutropenia with a certain causal relationship, causative drugs were cimetidine, dipyrone, sulphasalazine, methyldopa, spironolactone, propylthiouracil (2), thiamazole, sulphamethoxazole with trimethoprim, gentamicin, a combination preparation containing aminophenazone, benzylpenicillin and indomethacin. The individual drugs most often reported to cause agranulocytosis or neutropenia were: dipyrone (19), mianserin (15), sulphasalazine (13), sulphamethoxazole with trimethoprim (11), the group of penicillins (9), cimetidine (8), the thiouracil derivatives (8), phenylbutazone (8), and penicillamine (8). Agranulocytosis is a serious and fairly frequently reported adverse reaction. The reporting system of the Drug Safety Unit can be used very well for signal generation concerning adverse reactions to drugs. Am. J. Hematol. 57:206–211, 1998.

Key words: agranulocytosis; adverse drug reaction; dipyrone; mianserine; sulphasalazine

INTRODUCTION

Although agranulocytosis has many causes, the proportion attributable to drugs is substantial. Agranulocytosis was first associated with drugs by Madison and Squier [1]. Knowledge as to which drugs cause agranulocytosis is mainly based on case reports. As agranulocytosis is such a rare adverse reaction, only few epidemiologic studies have been performed on this subject. However, it is a very serious reaction, with a case-fatality rate of up to 32% [2]. It is, therefore, very important to know which drugs are capable of inducing agranulocytosis.

The Drug Safety Unit of the Dutch Inspectorate for Health Care (DSU) received 425 reports of drug-associated agranulocytosis, neutropenia, or leukopenia in the years 1974 to 1994. In this paper we give a description of these reports and discuss the proposed mechanism of agranulocytosis of each drug.

MATERIALS AND METHODS

The DSU runs a voluntary reporting scheme for suspected adverse reactions to drugs. Reports of the years 1974 to 1994 were used for this study. All reports with a diagnosis of agranulocytosis, granulocytopenia, neutro-

*Correspondence to: Dr. B.H.Ch. Stricker, Pharmacoepidemiology Unit, Department of Epidemiology and Biostatistics, Room Ee 2132, Erasmus University Medical School, Dr. Molewaterplein 50, 3015 GE Rotterdam, The Netherlands.

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penia, leukopenia, pancytopenia, bone marrow aplasia or depression, and myeloproliferative disorder were analysed according to a two-step procedure.

Firstly, every report was classified by the first author as to probability of agranulocytosis and the probability that agranulocytosis was caused by a drug according to the following criteria: In order to be classifiable, age and gender of the patient, and the number of leukocytes during the adverse reaction had to be known. Furthermore, if the total number of neutrophils was unknown and the total number of leukocytes was $> 1.5 \times 10^9$/l, the report was unclassifiable. *Agranulocytosis* or *neutropenia* were considered probable, if the nadir of the total number of neutrophils was $\leqslant 0.5 \times 10^9$/l or $> 0.5 \times 10^9$/l but $\leqslant 1.5 \times 10^9$/l, respectively, and (unless the patient died) the patient recovered after discontinuation of the drug. Bone marrow examination, if performed, had to show normal red cell lines and megakaryocytes. The hemoglobin had to be $\geqslant 6.5$ mmol/l and the number of thrombocytes $\geq 100 \times 10^9$/l. If the nadir of the total number of neutrophils was $\leqslant 0.5 \times 10^9$/l or $> 0.5 \times 10^9$/l but $\leqslant 1.5 \times 10^9$/l, and if also agranulocytosis respectively neutropenia were considered possible the patient recovered after discontinuation of the drug, but the result of bone marrow investigation was unknown, as were hemoglobin and the number of thrombocytes. If the report mentioned ''absolute'' or ''total'' agranulocytosis, this was interpreted as the complete absence of neutrophils. If there was only a bone marrow investigation on autopsy showing no neutrophils and the absolute number of neutrophils in the peripheral circulation was unknown, the report was nevertheless classified as *agranulocytosis probable* if the number of megakaryocytes and red cell precursors was normal. If the total number of neutrophils was $> 1.5 \times 10^9$/l, or Hb, Ht, or thrombocytes were abnormal (see above), or bone marrow investigation was not consistent with agranulocytosis, agranulocytosis was considered unlikely.

Secondly, the causal relationship between agranulocytosis or neutropenia and the drugs used was classified. The causal relationship between drug and agranulocytosis was classified as probable, if the drug had been used during the 10-day period prior to the first symptoms of agranulocytosis (challenge), if the patient had recovered on discontinuation (if he or she survived) (dechallenge), and if there was only one possible cause of agranulocytosis. If use of the drug had been continued and the patient recovered nevertheless, the drug was not considered as causal. Furthermore, the patient should not have used cytostatic drugs, immunosuppressive agents, or radiotherapy within 6 weeks prior to the onset of agranulocytosis. Also, there should not be a systemic disease that could have given rise to neutropenia, a neoplasm or granulomatous disease affecting the bone marrow, or any other disease presenting as agranulocytosis. If, in addition, there had been a positive reaction to rechallenge or a positive lymphocyte stimulation test, the causal relationship was classified as certain. If there was more than one possible cause of agranulocytosis, the causal relationship of each of these was classified as possible. In any other case, the causal relationship was classified as unlikely.

RESULTS

In the years 1974 to 1994, the DSU received 425 reports of agranulocytosis (n = 225), neutropenia (n = 58), or one of the other aforementioned diagnoses associated with drug use (n = 142). This group of 425 consisted of 149 men and 271 women. The gender of 5 persons was unknown. Of these 425, 112 were unclassifiable because age or gender of the patient or the total number of leukocytes at the time of the adverse reaction was unknown. Of the remaining 313 reports, 100 were classified as agranulocytosis probable, 78 as agranulocytosis possible, 8 as neutropenia probable, and 20 as neutropenia possible, whereas in 107 reports agranulocytosis was considered unlikely, mostly because the clinical picture suggested generalised bone marrow depression. In the further analysis, only the 206 reports of agranulocytosis or neutropenia will be considered. These consisted of 72 men and 134 women, with a median age of 56 (25–75%: 39–69 years) and 64 years (25–75%: 48–73 years), respectively. In 25 patients, the course of the adverse event was fatal (12%) (Table I). Three patients, however, after recovery from agranulocytosis, died due to concomitant illnesses. Four patients had not yet fully recovered at the time of reporting. Of ten patients, the outcome was not known. In 35 reports, the suspected drug had been used before but this was not stated in the majority of reports. Eleven patients had had the same adverse reaction to the suspected drug before, and in these cases the causal relationship was classified as ''certain.'' Almost 90% of all drugs had been used orally.

The most common symptoms were fever (106 patients), throat ache, pharyngitis, or tonsillitis (28 patients), sepsis (27 patients), stomatitis or glossitis (21 patients), pneumonia, bronchitis, or respiratory insufficiency (18 patients), exanthema or rash (17 patients), and skin infection, erysipelas, or furunculosis (12 patients). Symptoms were not stated in 66 reports.

Causes of agranulocytosis and neutropenia are listed in Table II, divided by classification (probable and possible), and causal relationship between exposure and outcome. There were 11 reports of probable agranulocytosis and 2 of probable neutropenia in which the causal relationship between drug and event was classified as ''certain.'' The causative drugs were cimetidine, dipyrone, salazosulfapyridine (sulfasalazine), methyldopa, spironolactone, propylthiouracil (n = 2), thiamazole, cotrimoxazole, gentamicin, and a combination preparation

TABLE I. General Descriptives of the Study Population (n = 206)

	Agranulocytosis probable	Agranulocytosis possible	Neutropenia probable	Neutropenia possible	Total (%)
Course					
Died	11	12	1	1	25 (12)
Fully recovered	85	58	6	18	167 (81)
Unknown	4	8	1	1	14 (7)
Suspected drug used previously					
Yes	17	13	2	3	35 (17)
No	—	3	—	—	3 (1)
Unknown	83	62	6	17	168 (82)
Previously same reaction to suspected drug					
Yes	6	3	1	1	11 (5)
No	4	7	1	1	13 (6)
Unknown	90	68	6	18	182 (88)

containing aminophenazone. The drugs causative of neutropenia were benzylpenicillin and indomethacin. The individual drugs most often reported to cause agranulocytosis or neutropenia were: dipyrone (n = 21), mianserin (n = 15), salazosulphapyridine (n = 13), cotrimoxazole (n = 11), the group of penicillins (n = 9), cimetidine (n = 8), the thiouracil derivatives (n = 8), phenylbutazone (n = 8), and penicillamine (n = 8).

DISCUSSION

This study reviews all reports of agranulocytosis and neutropenia during 20 years of reporting in The Netherlands. Several drugs are already well-known causes of agranulocytosis, such as the thiouracil derivative, carbimazole and thiamazole, dipyrone, salazosulphapyridine, and several anti-arrhythmic agents.

When looking at the numbers of reports of agranulocytosis or neutropenia due to a certain drug, a high number could erroneously suggest a high incidence rate. Firstly, the numbers of reports of agranulocytosis and neutropenia are accumulated over the whole period. As not all drugs were on the market for the full 20 years, cases of agranulocytosis to some drugs had to accumulate over much shorter periods. Secondly, sales figures of drugs differ enormously. If drug A is used more often than drug B, and the percentage of patients developing an adverse event is similar to both drugs, one would expect more reports of adverse events due to drug A than to drug B. This is generally true, but, thirdly, reporting bias may occur. When a drug is newly marketed, for instance, a relatively high percentage of adverse events is reported. This may also occur after a newly recognized adverse reaction is published in the medical literature. When a drug is widely known to cause a certain adverse event, however, the number of reported events usually declines. Fourthly, when estimating an incidence rate on the basis of reporting data and sales figures, this is invariably underestimated because of underreporting and because sales figures are always higher than the real amount of drugs used in the population. Therefore, reporting data cannot be used to compare drugs with respect to the incidence rate of agranulocytosis, but can be used for hypothesis generation. However, in a study on all admissions due to drug-associated agranulocytosis in The Netherlands, we were able to estimate the incidence of drug-associated agranulocytosis leading to hospital admission. The incidence we found varied from 1.6 to 2.5 per million inhabitants over the years 1987 to 1990 [3].

Few case series as large as this study have been published. This is inherent to the rarity of the adverse reaction. Case reports were published on all drugs listed as being frequently reported to the DSU in this article, e.g., mianserin, salazosulphapyridine, phenylbutazone, penicillamine, and dipyrone [4], the group of penicillins [5], cimetidine [6], naproxen [7], and the thiouracil derivatives [8,9], but also on drugs that were less frequently reported as a cause, such as clozapine [10–12], cephalosporins [13], procainamide [14], dapsone [15,16], paracetamol [17], and ticlopidine [18]. The DSU published case reports and case series on agranulocytosis attributed to aprindine [19,20], spironolactone [21], ticlopidine [22], propylthiouracil [23], pirenzepine [24], trazodone [25], and omeprazole [26], and on leukopenia attributed to mianserin [27].

Other Adverse Drug Reaction Reporting Systems have also published case series on agranulocytosis. The Swedish Adverse Drug Reporting Committee published two reports on drug-induced blood dyscrasias [2,28]. Dipyrone and antithyroid drugs seemed to cause agranulocytosis most commonly, but also sulphonamides were a frequent cause of all types of drug-induced blood cell disorders. The mortality rate among the cases of agranulocytosis was 32%, which is higher than the 12% in our study. This high figure, however, may be due to reporting bias, as serious cases are more readily reported. A case-history study of drug-induced blood disorders was performed at the Group Health Cooperative of Puget

TABLE II. Causes of Agranulocytosis/Neutropenia (206 Patients, More Than One Cause Per Patient Possible)*

Drug	Agranulocytosis/ neutropenia probable		Agranulocytosis/ neutropenia possible		Total (total agranulocytosis)
	A	B	A	B	
Dipyrone	7	5	4	5	21 (17)
Mianserin	8	2	2	3	15 (13)
Salazosulphapyridine (sulphasalazine)	6	1	4	2	13 (13)
Co-trimoxazole	5	1	1	4	11 (10)
Anti-arrhythmic agents[a]	4	1	4	1	10 (10)
Penicillins[b]	4	1	3	1	9 (8)
Thiouracil derivatives[c]	4		3	1	8 (8)
Phenylbutazone	2	2	2	2	8 (8)
Cimetidine	1	3	4		8 (7)
Penicillamine	1	2	1	4	8 (7)
Diclofenac		3	3	1	7 (5)
Carbamazepine	2	1	4		7 (5)
ACE-inhibitors[d]	2	1	3		6 (6)
Hydrochlorothiazide with potassium sparing diuretics		3		3	6 (6)
Indomethacin	1	1		4	6 (3)
Cephalosporins[e]	1	1	1	2	5 (5)
Oxyphenbutazone	1		3	1	5 (5)
Nitrofurantoin	2	1	1	1	5 (4)
Salicylic acid derivatives		1		4	5 (4)
Clozapine	2	1	2		5 (4)
Carbimazole	1		3	1	5 (2)
Sulphonylurea derivatives[f]		2		2	4 (4)
Methyldopa	1	1		2	4 (4)
Thiamazole	2		2		4 (4)
Nucleosides				4	4 (4)
Aminoglutethimide	2	1		1	4 (4)
Ibuprofen		2	1	1	4 (4)
Pentazocine		1		3	4 (3)
Levamisole	2		2		4 (3)
Promethazine	2	2			4 (3)
Chloramphenicol		2		1	3 (3)
Paracetamol and combination preparations		3			3 (3)
Perazine		1	1	1	3 (3)
Mebhydrolin	2	1			3 (3)
Ranitidine	1			2	3 (2)
Imipramine	1		2		3 (2)
Other drugs (all mentioned twice or less)[g]	14	13	10	12	49 (42)
Total	81	60	66	69	276 (241)

*A = causal relationship certain or probable; B = causal relationship possible.

[a]Procainamide (2), ajmaline (1), tocainide (1), aprindine (5), and amiodarone (1).

[b]Amoxycillin (1), azlocillin (1), benzylpenicillin (3), phenethicillin (1), cloxacillin (1), and penicillin (2).

[c]Methylthiouracil (1) and propylthiouracil (7).

[d]Captopril (5) and enalapril (1).

[e]Cephalexin (1), cephazolin (1), cefuroxime (1), cefotaxime (1), and cephradine (1).

[f]Glibenclamide (1) and tolbutamide (3).

[g]Phenytoin (2), chlorthalidone (2), sulphamethizole (2), norfloxacin (2), naproxen (2), clomipramine (2), trazodone (2), omeprazole (2), alimemazine (2), pirenzepine, ticlopidine, ibopamine, hydralazine, nifedipine, spironocatone, nalidixic acid, doxycycline, clindamycin, gentamicin, fusidic-acid, dapsone, azapropazone, combination preparations with aminophenazone, respectively, propyphenazone, sulindac, piroxicam, pirprofen, niflumic acid, allopurinol, glafenine, valproate, levodopa with carbidopa, chlorpromazine, haloperidol, zuclopenthixol, zopiclone, cinnarizine, metronidazole, combination preparations with pyrimethamine, and theophylline.

Sound, consisting of 225,000 members, over the period 1972 through 1981 [29]. They found 7 hospitalized patients with a granulocytopenia attributable to drugs, of which 4 were attributable to salazosulphapyridine. There were 875 patients using salazosulphapyridine during this period.

Epidemiologic studies have been performed on several drugs. Arneborn and Palmblad studied 133 patients admitted because of neutropenia in the Stockholm region (1,490,000 inhabitants) over the period 1973–75 [30]. Of these, 45 cases were probably drug-induced, giving an annual incidence of 0.001%. When they repeated this study over the years 1976–77 [31], the mortality rate was 27%, higher than in the first study (2%). The most frequent causes of agranulocytosis were sulphonamides, antithyroid drugs, and phenothiazines. An overview over the period 1973–78 related some of the incidence figures to sales figures [32]. The highest frequency was found for thenalidine, followed by thyreostatics, penicillamine, and sulphonamides. Only 35% had been reported to the authorities. The mortality rate was 11%.

The largest study performed was the International Agranulocytosis and Aplastic Anemia Study (IAAAS), an international case-control study, in which cases and controls were collected from 1980–86. Community-acquired patients (362) were found, which were compared with a control group. Comparing analgesics, positive associations were found for phenylbutazone, oxyphenbutazone, indomethacin, and dipyrone, but there was considerable variation by region for dipyrone, which the authors could not fully explain [33]. The authors also found an excess risk for antithyroid drugs [34]. Comparing anti-infective drugs, positive associations were found for co-trimoxazole and macrolides [35]. When analysing the data for cardiovascular drugs, a positive association was found for propranolol, dipyridamole, digoxin, acetyldigoxin, cinepazide, procainamide, and aprindine [36]. The IAAAS has been criticized in several publications [37–42] with regard to methodology. Ibanez et al. continued the data collection that had started because of the IAAAS and reported on antiarrhythmic drugs over the period 1980–1988. A relevant risk was found only for aprindine [43].

CONCLUSIONS

The drugs most often reported as a cause of agranulocytosis or neutropenia in our study were mianserin, salazosulphapyridine, co-trimoxazole, dipyrone, the group of anti-arrhythmic agents (notably aprindine), the group of penicillins, cimetidine, the thiouracil derivatives, phenylbutazone, and penicillamine. Despite years of experience, remarkably few epidemiological data exist on this topic. Further study should focus on the incidence rate of drug-induced agranulocytosis or neutropenia and compare them with other drugs used for similar indications.

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